PART X CHAPTER Y

Coffee antioxidants in chronic diseases

M.D. del Castillo^{1*}, A. Iriondo-DeHond¹, B. Fernandez-Gomez¹, N. Martinez-Saez¹, M. Rebollo-Hernanz¹,
M.A. Martín-Cabrejas¹, A. Farah²

¹Institute of Food Science Research (UAM–CSIC), Nicolás Cabrera 9, 28049 Madrid, Spain

²Instituto de Química, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil

*Corresponding author. E-mail: mdolores.delcastillo@csic.es

Abstract

Oxidative stress is associated to the risk of developing chronic diseases. A diet rich in antioxidants has been proposed as a habit to achieve an effective reduction of chronic diseases. Coffee is one of the most consumed beverages worldwide. The regular intake of coffee (three cups per day) may provide 1 g of chlorogenic acid which is a powerful dietary antioxidant. However, other natural compounds present in the green bean which resist roasting conditions also contribute to the overall antioxidant properties of the beverage prepared from roasted beans. In addition, the roasting process dramatically affects the chemical composition of green beans giving rise to coffee processing antioxidants. The present chapter pretends to make an updated overview of those antioxidants so far identified in the coffee beverage, their impact in the antioxidant defense *in vivo* and in chronic diseases. Coffee drinking slightly reduces the risk of developing some chronic diseases, therefore, this habit should be considered in healthy lifestyle recommendations. In this way, this common behavior could be of significant public health importance.

X.1. Introduction

Coffee brews in most countries provide the highest amount of antioxidants in the daily diet. The coffee brew is a mixture of bioactive compounds with potential antioxidant properties (Figure X.1).

[Figure X.1. near here]

Green coffee is composed primarily of water, carbohydrates, proteins and free amino acids, lipids, minerals, organic acids, phenolic compounds including chlorogenic acids, trigonelline, melatonin and caffeine, vitamins, minerals and fiber. Of these compounds found in green coffee, chlorogenic acids, caffeine, melatonin, fiber, minerals, vitamins and diterpenes are most likely to be antioxidants. Most of them can resist roasting and are present in the coffee brew produced from roasted coffee beans.

Antioxidant capacity is a comprehensive evaluation of the combination of individual antioxidants that occur naturally in foods.¹ The antioxidant capacity of coffee brews is generally associated with the presence of phenolic compounds, primarily in the form of chlorogenic acids.² Other compounds present in coffee formed during roasting “**coffee processing antioxidants**”, such as Maillard reaction products, mostly in the form of melanoidins,³ other phenolic compounds such as isoflavones, lignin and lignols, tocopherols,^{4–6} minerals,⁷ melatonin⁸ or caffeine⁹ also present antioxidant potential. Brew antioxidant profile significantly varies according to blend, roasting degree, grind, and method of preparation. Natural and formed antioxidants during coffee brewing process are revised in the present chapter.

The antioxidant capacity of coffee has been attaining a lot of attention, especially due to the convenience of their consumption and their potential health benefits. Several studies have compared coffee antioxidant efficacy with that of other beverages and revealed that coffee has an important contribution to the dietary antioxidants intake.^{10,11} Actually, numerous studies have shown that coffee (roasted or brews) is replete of antioxidant compounds.

Different analytical methods have been developed in order to measure the antioxidant capacity or the individual antioxidants in coffee.¹² These procedures are frequently based on the inhibition of the oxidation of a suitable substrate by the antioxidant agent. Subsequently, the extent of the oxidation is measured by UV–Vis spectrometry, chemiluminescence, or fluorescence. Nonetheless, the evaluation of antioxidant properties of coffee is not as easy, indeed, many methods have been used to quantify its antioxidant capacity, but the utilization of different types of substrates, the analytical conditions, the chosen analytical method, among other factors, can affect the estimation of the antioxidant capacity.

An overview of coffee antioxidant capacity data is summarized in the work published by Yashin *et al.*, 2013. The authors of the review concluded that both antioxidant capacity and total antioxidant content of roasted coffee are

of the same level, as corresponding values for tea.¹³ Antioxidants are presumed to be the most probable beneficial ingredients in coffee.¹⁴

Even though the bioavailability and effectiveness of antioxidant compounds in the human body have to be considered when estimating their bioactive potential, the *in vitro* assessment of dietary antioxidant capacity through plant foods consumption is considered as an important tool to evaluate the association between the antioxidant intake and possible health benefits reported in epidemiological studies.¹⁵ A very recent study shows that coffee, among red wine, maté tea and açaí, is the main contributor to the total dietary antioxidant capacity in Brazil, the seventh world's largest economy.¹ Besides coffee processing, environmental conditions and also the geographical origin affect the antioxidant capacity of coffee.¹⁶

Food has a vital role in maintaining our health properly and also helps in the prevention and cure of diseases. Nowadays, more than 95% of all chronic diseases are caused by food choice, toxic food ingredients, nutritional deficiencies and lack of physical exercise. Food rich in nutrients builds health, and unhealthy food leads to several diseases. During the 20th century, our eating habits have changed drastically. In the last decades the market of functional foods has dramatically increased. Many plant extracts and natural compounds are emerging as functional candidates for the reduction of risk of non-communicable chronic diseases.¹⁷

Some intervention studies have correlated coffee consumption with an increase in the plasmatic antioxidant capacity.^{18,19} Nevertheless, this increment in the antioxidant capacity of plasma would not necessarily be only due to the intrinsic antioxidant capacity of coffee but also to the effect of some compounds of coffee in the modulation of antioxidant defenses, such as increasing glutathione and antioxidant enzymes levels.²⁰

Very recent studies presented by Grosso *et al.*, in the 10th World Congress on Polyphenol Applications (http://dx.doi.org/10.18143/JISANH_v3i4) concluded that among individual polyphenol classes, phenolic acids and stilbenes were heavily linked with MetS, lignans and stilbenes with waist circumference; phenolic acids with blood pressure and triglycerides and flavonoids with fasting plasma glucose. The study highlighted the challenge of assessing the absorption and different polyphenol bioactivity. It is still unclear the polyphenol doses that achieve beneficial effects on human health. Metabolism and absorption of bioactive compounds vary greatly across population due to different facts including gut microbiota. At the moment, phenols intake levels cannot be precisely defined. Several epidemiological studies also document the protective effect of coffee components in the risk of chronic diseases such as age related metabolic disorders associated to oxidative stress and inflammation.²¹

Another health benefit associated to coffee consumption is a reduced risk of type 2 diabetes. A relationship between coffee consumption and diabetes was described during the last decade, triggering many more observational, human intervention, and mechanistic studies.²² Diabetes affects 346 million people worldwide and the World Health Organization projects that diabetes deaths will double between 2005 and 2030.²³ Other potential

beneficial effects of coffee relate to cardiovascular diseases,²⁴ to the well-being of the nervous system,^{25–27} Parkinson's disease²⁸ and Alzheimer,²⁹ hepatoprotection³⁰ and weight loss.³¹ Oxidative stress, inflammation and lipid peroxidation lead to the development of these chronic diseases, which are the main cause of mortality all over the world. Coffee may reduce mortality risk by favorably affecting inflammation, insulin sensitivity and depression.³² In the next sections of the present chapter, the health promoting effects of coffee individual antioxidant classes are discussed.

X.2. Effect of natural coffee antioxidants in chronic diseases

X.2.1. Phenolic Compounds

X.2.1.1. Hydroxy-cinnamic acids

Coffee is one of the richest sources of phenolic compounds in the Western diet, and the most abundant phenolic compounds in coffee are hydroxy-cinnamic acids. The hydroxy-cinnamic acid family includes chlorogenic, caffeic, ferulic, coumaric, and sinapic acid. Hydroxy-cinnamic acids are considered very important phytochemicals due to their biological properties. Further insights into the mechanisms that dietary polyphenols follow on influencing human health have been very recently provided by speakers at the 10th World Congress on Polyphenol Applications in Porto, Portugal in 2016 (http://dx.doi.org/10.18143/JISANH_v3i4).

The most abundant phenolic compounds of the hydroxy-cinnamic family are chlorogenic acids (CGA) (up to 12% of solids) being 5-caffeoylquinic acid (5-CQA) the main CGA compound in coffee.³³

CGAs contribute to the antioxidant properties of roasted coffee. The amount of phenolic compounds present in green coffee beans is reduced during roasting since CGAs are sensitive to the high temperatures (180–250°C) reached during the roasting process. Non-roasted green coffee beans possess higher antioxidant capacity than roasted coffee beans. The degradation of CGAs is proportional to the intensity of the roasting conditions.³⁴ The amount of total CGAs in light and medium roasted coffees represents 40–50% of the content in the original green coffee beans, making this low temperature roasted coffee a significant source of dietary CGAs.^{35,36} Besides the degradation of total CGAs, chlorogenic acid lactones (CGLs) are formed during the roasting process. CGLs are of great interest since they have potential effects on brain function, independent of the pharmacological effects of caffeine.³⁷ The antioxidant properties of these coffee processing compounds are revised in the chapter X.3. of the present section.

CGAs are stable in saliva and in gastric fluids. Studies suggest that about 90% of CGA from coffee could be available to reach the gastrointestinal tract to be hydrolyzed by esterases and absorbed in the free form.³⁸ The remaining 10% of CGA is suggested to be early absorbed in the stomach by passive diffusion.³⁹ When CGAs reach the small and large intestine they are subjected to hydrolysis and metabolization by intestinal bacteria (see

chapter X.3.). Studies using Caco-2 cell monolayers reported that CGA colonic metabolites are uptaken in the intestinal mucosa cells by passive diffusion and by the intestinal monocarboxylate transporter (MCT).⁴⁰ It has been demonstrated that a significant rise in free caffeic acid levels in plasma takes place 1 hour after coffee brew administration. This study supports the fact that caffeic acid found in plasma is likely to be derived from the hydrolysis of chlorogenic acid in the gastrointestinal tract.⁴¹

Studies on the bioavailability of hydroxy-cinnamic acids in humans suggest that after being absorbed, they perform potential health effects by protecting from oxidative stress, inflammation and cytotoxicity. In this chapter, we focus on the antioxidant activity of hydroxy-cinnamic acids against oxidative stress.⁴² Because a large amount of chlorogenic acids are absorbed in the metabolized form, considerable attention has been focused on the biological effects of their metabolites in order to evaluate possible *in vivo* effects of chlorogenic acid-containing diets. The radical-scavenging activity capacity of the free form of hydroxy-cinnamic acids has been determined *in vitro* and caffeic acid has shown to have more antioxidant properties than ferulic and *p*-coumaric acid.⁴³

Hydroxy-cinnamic acids may exert their antioxidant activity through two mechanisms: 1) they have a direct effect on oxygen radical scavenging⁴⁴ and 2) they induce antioxidant enzymes.⁴⁵ Specifically, caffeic acid modulates cellular responses to oxidative stress protecting against lipid oxidation preventing cell damage of colon cancer cells and peripheral blood mononuclear cells exposed to hydrogen peroxide.^{46,47} On the other hand, ferulic acid reduces lipid peroxidation, DNA damage and increases the antioxidant status in nicotine-administered rats.⁴⁸ Finally, it has been determined that *p*-coumaric acid prevents lipid oxidation and also directly scavenges hydroxyl radical ions.⁴⁹

Epidemiological and experimental evidence increasingly suggests that coffee consumption is correlated to prevention or delay of degenerative diseases connected with oxidative cellular stress. For instance, it has been demonstrated that coffee is beneficial to prevent cardiovascular diseases.²⁴ At a cellular level, CGA and other hydroxy-cinnamic acids derived from plants are effective in preventing oxidative damage to rat cardiomyocytes, stabilizing their membranes and improving their energetic status.⁵⁰ Caffeic acid, the initial metabolite of CGA, had an antioxidant effect and decreased glucose levels in a diabetic mouse model. In this study, caffeic acid significantly increased superoxide dismutase, catalase and glutathione peroxidase and lowered glucose, demonstrating an *in vivo* antioxidant activity on this hydroxy-cinnamic acid.⁵¹

Dietary polyphenols can prevent the initiation step of cancer by the inhibition of DNA-damage caused by free radicals or carcinogenic agents.⁵² CGA decreases ROS generation and stimulated glutathione-S-transferase activity in mice epithelial JB6 cells, providing a protective role against carcinogens.⁵³ Therefore, polyphenols present in coffee could prevent the development of cancer. In fact, epidemiological studies show an inverse association between consumption of coffee and the risk of certain cancers.⁵⁴

Several studies have shown that CGA acts as a neuroprotective agent. In a murine model, CGA significantly protects animals against scopolamine induced amnesia via antiacetylcholinesterase and antioxidant activities.⁵⁵ CGA also exerts a cytoprotective action against α -synuclein-induced toxicity in catecholaminergic PC12 neuronal cells.⁵⁶ Epidemiologic studies show that coffee intake is associated with a significantly lower incidence of Parkinson's disease and Alzheimer disease.^{28,29} But further research is needed to identify which compounds are responsible for this effect and to determine if coffee bioactive compounds can really act as neuroprotective agents to prevent neurodegenerative diseases.

There is also epidemiological evidence that suggests that coffee consumption is associated with the prevention or delay of type 2 diabetes.⁵⁷ Studies carried out by Bakuradze *et al.* concluded that daily consumption of 3–4 cups of brew from a special Arabica coffee might exert health beneficial effects, by reducing oxidative damage, body fat mass and energy/nutrient uptake.⁵⁸

In conclusion, hydroxy-cinnamic acids present in coffee constitute an important source of biologically active polyphenols that possess great antioxidant capacity contributing to the prevention or delay of aging and degenerative chronic diseases.

X.2.1.2. Isoflavones

Although in minor amounts, there are other phenolic compounds with antioxidant and free radical scavenging properties also described in coffee, such as isoflavones. These compounds are estrogen-like molecules with a common 3-phenylchromen-4-one core structure, differing by substituents such as methoxy, hydroxy, and glucoside functions. Few reports exist on these compounds in coffee but their contents in coffee beverages have been determined by gas and liquid chromatography coupled to mass spectrometry.⁵⁹ The principal isoflavones are genistein (5,7-dihydroxy-3-(4-hydroxyphenyl)chromen-4-one), daidzein (7-hydroxy-3-(4-hydroxyphenyl)chromen-4-one), glycitein (7-hydroxy-3-(4-hydroxyphenyl)-6-methoxychromen-4-one), formononetin (7-hydroxy-3-(4-methoxyphenyl)chromen-4-one) and biochanin A (5,7-dihydroxy-3-(4-methoxyphenyl)chromen-4-one).⁶⁰

The isoflavone contents in coffee beverages described in the literature are highly variable. Several factors, such as the method of preparation, the coffee species, and the roasting degree of coffee beans, have a great influence on the isoflavone profile of the coffee brew. However, it has been observed that biochanin A is always absent, and that formononetin is frequently the major isoflavone, followed by daidzein and genistein.⁶⁰

When isoflavones are consumed, they are hydrolyzed by gastric acids and also by bacterial glucosidases of the intestinal microflora. Sugar moieties are cleaved and aglycones released, which can be absorbed intact by enterocytes or further biotransformed by bacteria to specific metabolites which possess higher antioxidant

capacity than the initial glycosylated isoflavones, including equol and O-desmethylangolensin (metabolites of daidzein), and the nonoestrogenic p-ethylphenol (metabolite of genistein).⁶¹ Figure X.2 illustrates the metabolism of daidzin, one of the isoflavones found in coffee. It can be observed how glycosylated isoflavones after digestion become more antioxidant in the form of aglycosylated isoflavone metabolites.⁶² The clinical effectiveness of isoflavones in chronic diseases such as cardiovascular, bone and menopausal health, may be a function of the ability to biotransform these molecules to a more potent estrogenic isoflavone, equol.⁶³

[Figure X.2 near here]

Because of the structural similarity isoflavones have to β -estradiol, health benefits of isoflavones have been evaluated in age-related and hormone-dependent diseases.⁶⁴ However, in this chapter we focus on the antioxidant properties of these compounds. Previous studies indicated that the phenolic hydroxyl groups of isoflavones and their structural arrangements confer their antioxidant capacity through their H-donating properties. In fact, the total antioxidant activity of isoflavones gives a TEAC value nearly three times the antioxidant activity of Trolox or vitamin C.⁶⁵ In addition, the *in vitro* by the ABTS^{•+} radical cation assay showed the following order of antioxidant capacity genistein > daidzein = genistin = biochanin A.⁶⁶

Oxidative damage is associated with age-related diseases and the protective effects of dietary phytochemicals are often attributed to their antioxidant action.⁶⁷ There are a number of studies that have attempted to determine whether isoflavones exert antioxidant effects *in vivo*. In this sense, some authors have shown that the antioxidant activity of isoflavones against hydrogen peroxide production in HL-60 cells is genistein > diadzein > biochanin A.⁶⁸ Kapiotis and colleagues indicated that genistein is a potent antioxidant against LDL oxidation and it also protects against the cytotoxic effect of oxidized LDL.⁶⁹ It should be noted that these studies consider isoflavones contained in soy beans, but more studies are needed to determine if coffee isoflavones are biologically active and exert beneficial effects in human health.

Troxeutin, another isoflavone present in coffee, interacts and scavenges biologically important free radicals. Troxeutin exhibits cytoprotective ability as it protected different cell types (intestinal epithelial cells, fibroblasts and lymphocytes) exposed to oxidative stress. The protection offered by troxeutin may be by attenuating the damage to vital cellular molecules such as DNA, proteins & lipids, and restoration of cellular redox status.⁷⁰ Therefore, this molecule together with other isoflavones may find its application as an adjuvant in treating various diseases involving oxidative stress.

X.2.1.3. Anthocyanins

Other phenolic compounds present in coffee in minor amounts are anthocyanins. Anthocyanins are flavonoid compounds that act as plant pigments widely distributed in colored fruits, such as the coffee cherry. There is great interest in anthocyanins since they have potential health benefits due to their antioxidant properties. Anthocyanins are mainly located in the outer skin and in the pulp (byproduct named as “coffee husk”) of the coffee cherry, and are responsible for the red color of the coffee berry. Anthocyanins are also present in coffee seeds although in minor amounts.⁷¹ Therefore, coffee husks possess great potential as a natural source of anthocyanins.⁷²

The major anthocyanin in coffee pulp is cyanidin-3-rutinoside.⁷³ Another anthocyanin identified in coffee pulp is cyaniding-3-glycoside present in lower concentration⁷² (Figure X.3).

[Figure X.3 near here]

Apart from their coloring effects in fruits, anthocyanins show the ability to prevent lipid oxidation in human low-density lipoprotein (LDL) *in vitro*⁷⁴ and they also possess scavenging activity against various artificially generated free radicals.⁷⁵

Anthocyanins present in coffee cherries are reported to possess antioxidant properties. Murthy and colleagues are the only authors which have measured the total antioxidant activity of coffee anthocyanins⁷³. Cyanidin-3-rutinoside showed high antioxidant activity; exhibiting a higher reducing power than butylated hydroxytoluene (BHT) and ascorbic acid. Anthocyanins from coffee pulp showed good free radical scavenging activities and hence could be used as a nutraceutical and as a food supplement.⁷³ Therefore, coffee pulp may become an inexpensive and readily available source of natural colorants, dietary antioxidants and could be used as a nutraceutical and/or food supplement.

Guerra *et al.*⁷⁶ demonstrated anthocyanins bioactivity *ex vivo* showing the ability of cyanidin-3-glucoside to reduce the reactive oxygen species (ROS) production caused by aflatoxin B1 and ochratoxin A in human hepatoma cell line (Hep G2) and a human colonic adenocarcinoma cell line (CaCo-2).

The literature suggests that anthocyanins might have important health effects; however, basic aspects of their absorption and metabolism are not fully established. It has been suggested that anthocyanins are mainly absorbed from the stomach and small intestine under their glycosidic forms, and once absorbed through the intestinal barrier, they are partly hydrolyzed by intestinal β -glucosidases.⁷⁷ At present, there are no data concerning the bioavailability of coffee anthocyanins, so further research regarding this issue is of great interest since these compounds have beneficial effects on human health.

The potent antioxidant activity of anthocyanins is thought to play a major role in the beneficial health effects, which include maintenance of normal vascular permeability, vasoprotective and anti-inflammatory properties, protection against cancer and prevention of neural decay during the aging process.⁷⁸

X.2.2. Coffee indigestible phenols

X.2.2.1. Lignans

Lignans and neolignans are a large group of naturally occurring phenols which are widely extended in daily consumed foods such as coffee. Monolignols derived from hydroxy-cinnamic acids (*p*-coumaric, ferulic, and sinapic acids), are either dimerized to lignans in the cell or polymerized into larger lignin structures in the cell wall (Figure X.4).^{79,80} Although lignans are not classified as dietary fibers, they share some of the chemical characteristics of lignin, which is an insoluble fiber.⁸⁰

[Figure X.4 near here]

Lignans include a number of dimonolignols compounds such as secoisolariciresinol, lariciresinol, matairesinol and pinoresinol which are present in the coffee beverage (Figure X.7).^{81,82} Average lignan intake from coffee beverage was 6-1 mg/day, suggesting that lignans from this source are an important contributor to their daily intake.⁸² The nutritional significance of lignans is unknown.

Lignans are present in plants both as aglycones (without sugars) and as glycosides (with sugars). Lignan glycosides are absorbed in the gastrointestinal tract after metabolism by intestinal bacteria to lignan aglycones and the enterolignan enterodiols which are oxidized to the enterolignan enterolactone (Figure X.5). Initially, only secoisolariciresinol and matairesinol were considered to be enterolignan precursors⁸³, but recently, new precursors such as lariciresinol and pinoresinol were identified, all of them present in coffee.⁸⁴ The enterolactone and enterodiols have been detected in the blood and urine of both humans and animals, but only small amounts of plant lignans have been found in human urine.⁸⁵ The urinary excretion of plant lignans was largely explained by the intake of coffee in Finnish men.⁸⁵

[Figure X.5 near here]

Antioxidant activity seems to be one of mechanisms of action that are responsible for the bioactivity of plant lignans and their derived metabolites. For example, secoisolariciresinol and its derived metabolites enterodiols and enterolactone exert even higher antioxidant activity than that of vitamin E. The secoisolariciresinol diglucoside showed beneficial effects in cancer and lupus nephritis and these may be ascribed to the ability of secoisolariciresinol diglucoside to scavenge hydroxyl radicals.⁸⁶ The antioxidant activities of lignans and their metabolites have also been suggested to contribute to the reduction of serum cholesterol, lipid peroxidation and development of atherosclerosis in animals.^{87,88} Human studies showed that dietary intakes of lignans reduce the risk of cardiovascular diseases due to lipid and blood pressure lowering abilities.⁸⁰ These evidences indicate that consumption of lignans may reduce the risk of diseases related to oxidative stress such as cardiovascular diseases and T2D.

X.2.2.2. Lignins

Lignins are representative polyphenols in the plant kingdom. Lignins are polymers built from the p-coumaryl, coniferyl, and sinapyl hydroxycinnamic alcohols (monolignols) (Figure X.4).^{80,89} Lignins are important in plants because they exert different protection functions such as building the plant cell walls, aiding water transport, keeping polysaccharides in the plant cell walls from degrading, helping plants resist pathogens and other threats, and providing texture in comestible plants.⁸⁹ They are present in green and roasted coffee beans accounting for approximately 3% of the dry matter.⁵ Nutritionally, lignins are considered components of insoluble dietary fibre⁹⁰ and exhibit antioxidant properties.⁹¹ Thus, lignins are resistant to digestion in the small intestine and require colonic bacterial fermentation. Metabolites of native lignins have been reported to reduce oxidative stress and inflammation in streptozotocin-induced diabetic rats.⁹² Lignin-derived metabolites protected STZ-induced diabetic kidneys from oxidative stress, from the infiltration and activation of macrophages and from glomerular expansion.⁹³

X.2.2.3 Antioxidant coffee dietary fibre (interaction products phenol-lignin naturally occurring)

Lignin is considered as non-carbohydrate dietary fibre.⁹⁴ Previous reports showed that lignin were interfered by phenolic polymers which possess strong antioxidant properties.⁹⁵ On the other hand, phenol compounds may be bound to the structure of lignin providing antioxidant properties to the complex.⁹⁶

The transportation of dietary antioxidants through the gastrointestinal tract has been described as an essential function of dietary fibre.⁹⁷ Polyphenols linked to dietary fibre may be released in the colon by the action of bacterial microbiota, producing bioactive metabolites and an antioxidant environment, thereby reducing the risk of gastrointestinal diseases associated with oxidative stress and inflammation.

X.2.3. Alkaloids

Alkaloids are a group of phytochemicals containing basic nitrogen atoms. Coffee beans mainly contain three types of antioxidant alkaloids, caffeine, melatonin and trigonelline.

X.2.3.1. Caffeine

Besides CGAs, caffeine may be the most interesting compound with regard to its biological effects. Roasting does not notably reduce the content of caffeine even if some losses occur due to sublimation during the heating process,

when carried out at higher temperatures.⁹⁸ Brewing method influences caffeine content in the final beverage. Coffee grounds to water ratio, volume of prepared coffee and time of brewing play a significant role in the extraction of caffeine from coffee grounds. Grinding might also influence consumers' caffeine consumption.⁹⁹ Caffeine content in coffee brews can vary from 5.4 to 0.4 mg/mL, being higher in brews prepared by Italian or espresso coffeemakers, while the lowest values have been observed in filtered coffees.¹⁰⁰ Decaffeination process negatively affects antioxidant capacity,¹⁰¹ leading to a decrease in total antioxidant capacity values of ~25–30%, probably due to the antioxidant capacity of caffeine,¹⁰² but other compound losses, such as melatonin may also take part in this decrease.

Caffeine is rapidly and almost completely absorbed in the stomach and small intestine and distributed to all tissues, including the brain. The maximum concentration in serum is reached within 60 min after intake and the apparent $T_{1/2}$ of caffeine is 5 h.¹⁰³ Caffeine metabolism takes place primarily in the liver. Firstly, caffeine is demethylated leading to the three dimethylxanthines: paraxanthine, theobromine, and theophylline. These metabolites are then further demethylated in the liver to the corresponding monomethylxanthines before being oxidised to methyluric acids and other products (see chapter X.3).¹⁰⁴

Caffeine and its catabolic products theobromine and xanthine exhibit antioxidant properties.^{105,106} This molecule might contribute to the overall antioxidant capacity of coffee, being an excellent $\cdot\text{OH}$ scavenger;^{102,105} nevertheless, it was found that caffeine is inefficient for directly scavenging $\text{O}_2^{\cdot-}$ and $\cdot\text{OOCH}_3$ radicals and most likely other alkyl peroxy radicals. On the other hand, it is predicted to be a modest scavenger of $\cdot\text{OCH}_3$, and probably of other alkoxy radicals, and a poor scavenger of $\text{HOO}\cdot$.¹⁰⁷

Caffeine acts as a protector agent of cell membranes against oxidative damage, being an effective inhibitor of lipid peroxidation.¹⁰⁸ Neither caffeine nor its dimethylxanthine metabolites exhibited antioxidant activity while, in contrast, 1-methylxanthine and 1-methyluric acid, were highly effective antioxidants *in vitro* being able to prevent LDL oxidation.¹⁰⁹ Nevertheless, further studies demonstrated caffeine protection against *in vitro* LDL oxidation.¹¹⁰ Methylxanthines may also play a role, since these compounds have already shown an improvement vasodilation and cardiac-stimulation and HDL- cholesterol raising effects. All of these benefits of caffeine and their metabolites could prevent the risk of cardiovascular disease.

Caffeine and their metabolites play an outstanding role in lowering chronic disease risk like type 2 diabetes (T2D).^{21,111} Caffeine metabolites protected pancreas against oxidative stress in rats suffering streptozotocin-induced diabetes.^{112,113} Other authors have observed a protective effect of caffeine in apoptotic pancreatic beta cells.^{114,115}

Parkinson's disease is characterized by the degeneration of dopaminergic neurons in the substantia nigra. Epidemiological and animal studies suggest that caffeine consumption decreases the risk of Parkinson's disease by protecting against dopaminergic neurotoxicity.¹¹⁶

X.2.3.2. Melatonin

Melatonin is a small indolamine (Figure X.6) with numerous receptor-mediated and receptor-independent actions.¹¹⁷ Free radical scavenger and indirect antioxidant are among the most described actions for melatonin.^{118–120} About forty years ago, melatonin was removed as a by-product of the decaffeination process of coffee beans. This was the first indication of the presence of melatonin in plants or plant products. Then, it was not known that melatonin existed in plants; it was assumed that melatonin resulted from an unexpected chemical reaction, as a consequence of the decaffeination process.¹²¹ Long afterward, Ramakrishna *et al.*¹²² studied the content of this alkaloid in Robusta and Arabica coffees. Robusta green coffee beans showed 5.8 µg/g dry weight, content that was increased in the coffee bean during roasting, probably due to losses in the volatile fraction. In the same way, Arabica beans, with higher melatonin concentration, raised their content from 6.8 to 9.6 µg/g dry weight. These authors also evaluated melatonin content in decocted coffee brews, noticing how final concentration depends on the preparation method. Therefore, the influence of different brewing processes on the content of melatonin in the final beverage have been evaluated.¹²³ Espresso coffee brews presented the highest melatonin levels (0.12 µg/mL) followed by brews made with French press, filter and Italian coffeemakers. Thus, coffee might be a potential source of this compound since a cup of coffee would contain 3–6 µg of melatonin, being of nutraceutical value due to its promising antioxidant potential.

[Figure X.6 near here]

Melatonin and its derivatives have shown to be powerful direct free radical scavengers. Several mechanisms by which melatonin detoxifies oxidants are considered to be functioning, including single electron transfer, hydrogen transfer, and radical adduct formation.^{119,124} Besides direct scavenging of ROS/RNS, melatonin also stimulates antioxidant enzymes, suppresses pro-oxidant enzymes, and improves mitochondrial function thereby reducing radical formation.^{117,120,125}

Experimental evidence indicated that melatonin has potential to reduce the risk of T2D by protect beta cells against oxidative stress since it neutralizes the production reactive species and normalizes the redox state in the cell.¹²⁶

X.2.3.3. Trigonelline

Trigonelline is one of the major components of coffee beans, representing ~ 1-2% of the dry weight. Its content in coffee brews decreases as roasting degree increases.^{127,128} Amounts in coffee brew depends largely on the coffee making procedure and appear to range between 40 and 110 mg per serving.^{5,20}

Trigonelline absorption occurs initially in the stomach. It showed a maximum plasmatic concentration of 6 mM after 3 h and had an apparent $T_{1/2}$ of 5 h, after the consumption of a cup of coffee. Urinary elimination of trigonelline 0–8 h post-ingestion of coffee is ~52% of intake, showing that considerable quantities pass through the circulation without being subjected to phase II metabolism.¹²⁹

Trigonelline has demonstrated to present antioxidant properties. In this context, trigonelline showed a weak *in vitro* scavenging ability against DPPH radical, but not against the $\cdot\text{OH}$,¹³⁰ preventing liposome peroxidation.¹³¹ The alkaloid suppressed ROS-potentiated invasive activity of pre-treated rat hepatoma cells but did not scavenge intracellular peroxides,¹³² diminished DNA damage in Caco-2 cells¹³³ and increased cell viability against H_2O_2 induced stress, scavenging H_2O_2 mediated free radical productions.¹³⁴ Cells pre-treated with trigonelline significantly maintained the enzymatic antioxidant activity such as SOD, catalase and non-enzymatic antioxidant like reduced glutathione content.¹³⁴

In vivo studies have proven that treatment with trigonelline increases SOD and decreases lipid peroxidation end product, malondialdehyde, in diabetic male Wistar rats, reducing, therefore, oxidative stress.^{135–138} Treatment of rats with trigonelline produced an increase not only in SOD but also in catalase activity and glutathione content in pancreatic tissue¹³⁶ and in renal tissue, augmenting, hence, the intracellular antioxidant defense.^{137,138}

Therefore, coffee trigonelline may play an essential role on the prevention of chronic disorders thanks to its protective action against cellular DNA damage and oxidative stress.

X.2.4. Diterpenes

Cafestol and kahweol are two diterpenes exclusively found in coffee between a 0.1 to 1 mg/g of dry matter.¹³⁹ Diterpenes exhibit good stability at high temperatures, roasting does not reduce their content.¹⁴⁰

The amount of diterpenes content in a standard cup of coffee varies depending on the brewing technique; filtered coffees contained insignificant levels of them in the brew, as the paper filter in drip-filtered coffee retained the diterpenes.¹⁴¹ Scandinavian boiled coffee, French press and Turkish coffee contain from 6 to 12 mg per cup, whereas filtered coffee, and instant coffee contain less than 0.6 mg per cup.²⁰ Although espresso coffee exhibits high concentrations of kahweol and cafestol, it is considered as an intermediate source of these compounds (4 mg per cup) due to its small serving sizes.¹¹⁶

The superoxide scavenging properties of kahweol and cafestol evaluated in the xanthine/xanthine oxidase system indicated that they have free radical-quenching activity.¹⁴² Coffee diterpenes may protect as an antioxidant increasing glutathione synthesis.¹⁴³ A mixture of cafestol and kahweol has also shown to reduce both ROS levels and the extent of lipid oxidation in H_2O_2 -induced NIH3T3 cells.^{142,144} The incubation of hepatocytes with kahweol and cafestol resulted in the attenuation of tert-butyl hydroperoxide-induced cellular ROS production and DNA damage through its anti-oxidative effects.¹⁴⁵

Pretreatment of mice with kahweol and cafestol prior to carbon tetrachloride exposure effectively increased cellular glutathione concentration and reduced lipid peroxidation, two important indices of the prevention of ROS-induced cellular damage.¹⁴⁶ Kahweol and cafestol mode of action includes induction of phase II detoxifying enzymes, and regulation of Nrf2/ARE signalling pathways, thereby enhancing the endogenous defence systems against oxidative damage.^{54,147}

Beneficial effects of coffee diterpenes might be related to their antioxidant capacity by scavenging ROS and regulating antioxidant enzymes. Further clinical trials with human beings are required to support previous research.

X.2.5. Vitamins

X.2.5.1. Vitamin E (Tocopherols)

Tocopherols in coffee beans are lipophilic constituents present in the coffee oil, which possess antioxidant properties. The content of α -, β -, and γ -tocopherols varies between Arabicas and Robustas, exhibiting generally higher values in green Arabica beans.¹⁴⁸ The average amount of tocopherols in coffee has been reported as 11.9 mg/100 g green coffee.¹⁴⁹ Furthermore, tocopherol content significantly differs according to the origin. It has been shown that the amount of tocopherols in coffee brews depends on coffee species, the degree of roasting and method of preparation.⁶ α -, and β -Tocopherol content ranges from 15 to 126 or to 296 ng/mL, respectively.

Vitamin E is an efficient lipid soluble antioxidant that is incorporated into cellular membranes in which it effectively inhibits the peroxidation of lipids.¹⁵⁰ It functions as a 'chain breaker' during lipid peroxidation in cell membranes and various lipid particles including low-density lipoprotein. This vitamin functions intercepting lipid peroxy radicals (LOO $\cdot$) and terminating the lipid peroxidation chain reaction.¹⁵¹ α -Tocopherol can also inhibit oxidation of proteins.¹⁵² Estévez and Heinonen¹⁵³ demonstrated that α -tocopherol reduced the formation of α -amino adipic and γ -glutamic semialdehydes from oxidized myofibrillar proteins *in vitro*.

A synergistic effect has been observed when α -tocopherol and ferulic acid were combined. An effective antioxidant system against oxidation of liposomes was observed when these two compounds act in combination. This knowledge may be used to design better and more efficient protection systems of unsaturated fatty acids and other bioactive compounds against oxidation in liposomal carriers as drugs, food supplements, creams and cosmetics.¹⁵⁴

Therefore, vitamin E as an antioxidant compound prevents or delays chronic diseases associated with free radicals that might contribute to cancer development and cardiovascular pathologies¹⁵⁵. Further *in vivo* investigation is needed to gain insight into its biological effects on human health.

X.2.5.2. Vitamin B2 (Riboflavin)

Riboflavin survives through the roasting process, considering the high temperatures employed. Assays on beverages prepared from roasted coffee indicate that vitamins are easily extracted and present in measurable amounts (0.2-0.3 mg/100 g), although at rather low levels in relation to dietary requirements.¹⁵⁶

Glutathione reductase requires riboflavin in the FAD coenzyme form for its activity. Oxidized glutathione should be reduced by glutathione reductase to recover its antioxidant properties, the process in which riboflavin has a key role. Consequently, there is a possibility that riboflavin deficiency could affect the antioxidant properties of glutathione and lead to an impaired antioxidant status.¹⁵⁷

In vitro studies have also indicated that riboflavin itself has an antioxidant nature, independent of its action as the glutathione reductase coenzyme.¹⁵⁸ The suggested mechanism could be the deactivation of hydroperoxide through the reversion of riboflavin from the reduced form (dihydroriboflavin) to the oxidised form.¹⁵⁹

According to the findings of animal and human studies, riboflavin status appears to have an effect on the oxidative state of the body, in particular, on lipid peroxidation. However, it seems that the mechanism by which riboflavin can exert its antioxidant effect cannot result only of the glutathione redox cycle,¹⁵⁷ but also of its direct scavenging activity on free radicals.¹⁶⁰

Studies indicate that riboflavin protects organisms from oxidative injury after ischemia by the antioxidant character of this compound.¹⁵⁷ More research is needed in order to find out the effect of coffee riboflavin in chronic diseases.

X.2.6. Minerals

The mineral content in coffee is only about 5 % (m/m), however, the implications of several elements on the oxidative status might enhance their importance ⁷.

X.2.6.1. Selenium

The content of Selenium in coffee beans ranged from 0.01 to 5.8 $\mu\text{g g}^{-1}$.^{7,161,162} The body contains complex antioxidant systems that require adequate intake of selenium for normal physiological function. Se, in the form of selenocysteine, is a constituent of 25 classes of selenoproteins, including GPxs, and thioredoxins.^{163,164} There is evidence that several of these selenoproteins have antioxidant activities; the antioxidant properties of selenium compounds have been investigated in several clinical trials and other *in vivo* studies for disease prevention and treatment.¹⁶⁵ Se compounds are well known for their ability to scavenge ROS and may be able to catalytically decompose peroxynitrite.¹⁶⁵ Selenium can protect LDL against oxidation in a cell-free *in vitro* system and it significantly delayed the CuCl_2 - or AAPH-induced formation of conjugated dienes.¹⁶⁶

X.2.6.2. Copper

Diverse investigations have determined the content of copper in coffee beans, founding it in the range of 0.4–30.1. $\mu\text{g g}^{-1}$.^{7,162,167} Cu is part of SOD: copper/zinc SOD is found within most cells of the body, including red blood cells; and extracellular SOD is a copper-containing enzyme found at high levels in the lungs and low levels in plasma.¹⁶⁸ Furthermore, by binding copper, ceruloplasmin prevents free copper ions from catalyzing oxidative damage.¹⁶⁹

Depending on the circumstances, impaired antioxidant status could be either a primary or secondary factor involved in pathological damage during Cu deficiency, since Cu enzymes are involved in preventing free radical damage as well as maintaining structural integrity of tissues and energy production.¹⁶⁹

X.2.6.3. Zinc

The presence of Zinc in coffee is of relevance. Since in coffee grounds the content range 1.2–803 $\mu\text{g g}^{-1}$,^{7,161,162} coffee regular consumption could contribute to the recommended zinc intake.

Zn plays an important role in the structure of proteins; a finger-like structure, known as a zinc finger motif, stabilizes the structure of a number of proteins. For example, Zn plays a critical structural role for the antioxidant enzyme copper-zinc superoxide dismutase (CuZnSOD), while Cu provides the catalytic activity.^{170,171}

Numerous investigators have used chronic deprivation studies in an attempt to answer the question of whether zinc has a physiological role as an antioxidant. In general, long-term deprivation of zinc renders an organism more susceptible to injury induced by a variety of oxidative stresses.¹⁷⁰ The structure of cell membranes is affected by Zn deficiency by means of an increased susceptibility to oxidative damage which finally impair their function.¹⁷²

The acute antioxidant effects of zinc are generally manifested in the presence of a demonstrable short-term increase in levels of this metal. Basically two mechanisms have been described: sulfhydryl stabilization and reduction in the formation of $\cdot\text{OH}$ from H_2O_2 and O_2^- through the antagonism of redox-active transition metals.¹⁷³

The effect of the chronic administration of zinc is the clearest example of what is meant by an indirect effect linked to the induction of metallothioneins, a group of low-molecular-weight metal-binding proteins which display *in vitro* radical ($\cdot\text{OH}$) scavenging capacity.^{173,174}

X.2.6.4. Manganese

Manganese concentration in coffee ranged from 6.6 to 320 $\mu\text{g g}^{-1}$).^{7,161,162} Manganese superoxide dismutase (MnSOD) is the principal antioxidant enzyme in the mitochondria. Because mitochondria consume over 90% of the oxygen used by cells, they are especially vulnerable to oxidative stress. MnSOD catalyzes the conversion of superoxide radicals to hydrogen peroxide, which can be reduced to water by other antioxidant enzymes.¹⁷⁵

In addition to serving as a substitute for SOD, manganese-antioxidant, small non-proteinaceous complexes of manganese, can boost oxidative stress resistance. Moreover, the efficacy of manganese in this regard is reliant on a high manganese/iron ratio in the cell.¹⁷⁶

The antioxidant effects of manganese were studied as the inhibition of microsomal lipid peroxidation and crocin bleaching by peroxy radicals. Mn(II) was the most active antioxidant mineral among the studied. Thus, Mn reduced the production of MDA and exhibited chain-breaking antioxidant capacity, related to the rapid quenching of peroxy radicals, due to the high rate constant of the interaction of Mn(II) with peroxy radical ($\text{ROO}^\bullet + \text{Mn(II)} + \text{H}^+ \rightarrow \text{ROOH} + \text{Mn(III)}$).¹⁷⁷

More research is needed to study the efficacy of minerals present in coffee under biologically relevant conditions in order to identify antioxidant therapies for the treatment and prevention of diseases caused by oxidative stress.

X.3. Effect of coffee processing antioxidants in chronic diseases

Different chemical reactions such as pyrolysis, caramelization, and Maillard reaction occur in the coffee bean during roasting giving rise to new antioxidants hereby coined as “coffee processing antioxidants” (Figure X.7). The composition of the coffee bean changes dramatically since some compounds are destroyed and others are neo-formed. Substances of high and low volatility appear in the roasted coffee, which are important for the aroma and flavor of the brew as well as bioactive compounds presenting antioxidant and other biological properties.⁵ Coffee processing antioxidants can be nonvolatile and volatile.

[Figure X.7 near here]

X.3.1. Nonvolatile compounds of roasted coffee

X.3.1.1. Melanoidins

Coffee melanoidins are high molecular weight (HMW), brown colored, polymeric substances that are formed during the final Maillard reaction in the coffee roasting; contributing up to 25% of the brewed coffee dry matter.³ The structure of coffee melanoidins is hindered by the enormous complexity and diversity of their structures

besides the difficulty in isolation of pure melanoidin fractions. Carbohydrates, proteins¹⁷⁸ and phenolic compounds have been suggested as components of the coffee melanoidins¹⁷⁹

The formation of melanoidins during coffee roasting appears to compensate for any possible loss of antioxidants compounds and to maintain the level of antioxidant capacity of coffee.¹⁴⁴ The melanoidins have showed to contribute in 20% of the whole antioxidant capacity of the coffee brew.¹⁸⁰

In order to exhibit biological properties in the organism, apart from the effect inside the gastrointestinal tract, coffee melanoidins must be bioavailable. In general, the bioavailability of HMW Maillard reaction products (MRPs) is assumed to be highly limited, whereas for low molecular MRPs substantial amounts can be detected in the urine after dietary intake.¹⁸¹

In vitro gastrointestinal digestion of coffee melanoidins¹⁸² showed partial resistance to the digestive enzymes as 86% kept undigested. The remaining 14% was released as low molecular weight (LMW) compounds (<10 KDa) presenting antioxidant capacity up to 8 times higher than that of their parent coffee melanoidin. These released LMW compounds could then be bioaccessible to be absorbed. Other authors (Faist & Erbersdobler, 2001 and references therein) described urinary excretion of HMW melanoidins and LMW premelanoidins at 4.3% and 27%, respectively, in animal model of rats. The analysis of feces showed values from 87% to 61% for HMW and LMW fractions, respectively. In addition, the HMW melanoidin fraction in the diet seemed to be degraded into LMW fractions by intestinal microorganisms and absorbed in the intestine.¹⁸⁴ These findings reinforce the idea that both LMW and HMW compounds are absorbed at least partially, developing specific bioactivity *in vivo*.

The mechanisms of antioxidant action of melanoidins have been attributed to scavenging hydroxyl and peroxy radicals, respectively, breaking the radical chain by donation of hydrogen.^{185–187} The presence of LMW compounds linked non-covalently to the melanoidin skeleton contributes significantly to the peroxy radical scavenging capacity attributed to coffee melanoidins.¹⁸⁶ In addition, the other mechanism of action is the metal chelating capacity and also to chelating pro-oxidant transition metal ions. Coffee melanoidins can chelate different pro-oxidant metal species, then inhibiting lipid peroxidation during gastric digestion.¹⁸⁸ Some studies centered the chelating ability on the hydroxyl groups of pyranone groups, although others focused on the type of sugar residues or degradation products of CGAs in the polymer structure.^{188,189} On the other hand, the antioxidant capacity includes the activation of redox transcription factors and upregulation of genes that induce the expression of antioxidant enzymes *in vivo*.¹⁴⁴

The antioxidant activity of coffee melanoidins has been widely reviewed on cell culture and animal models.^{144,179,190} Goya *et al.* (2007)¹⁹¹ reported protection against oxidative stress in human hepatocytes HepG2 treated with digested coffee melanoidins at physiological concentrations. Increased cellular activities related with the antioxidant defense such as glutathione (GSH) and the lowering of a secondary lipid oxidation product, malondialdehyde (MDA) were achieved. Another study showed an increased survival rate of human

neuroblastoma cells IMR32 pretreated with H₂O₂ caused by melanoidins with molecular weights greater than 3.5 kDa, recovered from dark roasted coffee beverage.¹⁹² In addition, coffee melanoidins (>12 KDa) exhibited protective effects against liver oxidative stress in rats fed with high fat and calorie diets. The reduction of pro-inflammation in the liver was determined by the corresponding elevation of specific anti-inflammatory cytokine biomarkers.¹⁹³

In consequence, health benefits have been associated to this antioxidant character of coffee melanoidins.¹⁷⁹ Intake of coffee melanoidins through the coffee beverage may provide protective effect against oxidative damages¹⁹¹ and radical stress in the gut¹⁹⁴ which is associated with the development of colon cancer.¹⁹⁵ Furthermore, the ability of melanoidins to inhibit the lipoxidation might contribute to enhance human health, since products from the lipoxidation are related to the development of atherosclerosis and other chronic diseases.¹⁹⁶

In conclusion, melanoidins present in coffee comprise great biological activity relative to their antioxidant properties that may contribute to the prevention or delay of chronic diseases.

X.3.1.1.1 Coffee Maillardized dietary fiber

Melanoidins have been proposed as a type of soluble Maillardized dietary fiber¹⁹⁷ It is very complex to structurally separate fiber from melanoidins and vice versa because carbohydrates are integral components of coffee melanoidins.¹⁸⁹ A primary skeleton of melanoidins is constituted by carbohydrates, including dietary fiber, polyphenols, and proteins. Later and according to the extent of roasting conditions, the complexity of this primary structure increases and new LMW compounds are linked to the melanoidin skeleton backbone. Then, soluble dietary fiber progressively turned to a melanoidinic structure (45%, w/w) during roasting.

The polysaccharide profile could exhibit physiological antioxidant activity¹⁸⁸ and due to its richness in phenolic compounds, antioxidant activity might be exerted *in vivo*. This coffee Maillardized dietary fiber can act as an antioxidant dietary fiber, quenching the radical species that are generated continuously within the gut and therefore, maintaining the reducing environment inside the gastrointestinal tract.¹⁸⁸ Further studies are required to evaluate the effect of these coffee melanoidins as soluble Maillardized dietary fiber on the prevention of chronic diseases such as intestinal inflammatory diseases and T2D.

X.3.1.2. Lactones

CGA lactones (CGLs) or quinides are formed during the roasting process of the coffee by loss of a water molecule from the quinic acid moiety and formation of an intramolecular ester bond. They are formed by less than 10% of CGAs and about 30% of the possible precursors in green coffee.¹⁹⁸ CGLs contribute considerably to the bitterness

of the coffee beverage. The main CGA lactones formed in coffee are the 1,5-lactones -3-caffeoylquinic acid lactone (3-CQL) and 4-caffeoylquinic acid (4-CQA) (Figure X.7).

In addition, to nine CGAs in green coffee, seven CGLs have been identified in roasted coffee. Farah *et al.*¹⁹⁸ reported the highest content of CGLs approximately after 7 min of the roasting process and maximum values of 398 mg/100 g and 424 mg/100 g of coffee for *C. arabica* and *C. canephora*, respectively, which corresponded to 7.3% and 5.6% of total CGAs in green Arabica and Robusta coffee. Despite the higher content of 4-caffeoylquinic acid (4-CQA), as compared to 3-caffeoylquinic acid (3-CQA) in green beans, 3-CQL is the major lactone, reaching its maximum amount at 7 min of roasting. The optimum degree of roasting to achieve a maximum content of lactones in coffee is light–medium roast.¹⁹⁸

Regarding the bioavailability of CGLs, Farah *et al.*¹⁹⁹ described that part of the lactone administered via gavage to rats was recovered in the form of CGA. This finding was confirmed by an *ex vivo* study in which a percentage of the major 1,5-caffeoylquinic acid lactones (CQLs) was converted into caffeoylquinic acids after contact with the alkaline pH of human digestive fluids (unpublished). Therefore, it is likely that a large proportion of these lactones consumed in the brew return to their respective CGA forms during digestion, indirectly increasing the total CGA intake. Therefore, the mechanism of action may be partially that described for CGAs in section X.2.1 and might exhibit related antioxidant properties.

Moreover, other studies have reported traces of sulfated CGLs detected in plasma and urine of human subjects after consumption of 200-ml serving of instant coffee containing caffeoyl acid lactones comprising 14% of total CGAs and 0.2%–0.3% of the coffee.^{200,201} Maximum plasma concentrations were achieved within 1h of coffee intake, in particular 0.6 and 0.7 h, for 3-CQAL-O-sulfate and 4-CQAL-O-sulfate, respectively. This short duration indicates absorption of these lactones by the small intestine. Rapid elimination from the circulatory system was also detected, with a half-life elimination time of 0.4 and 0.5h for 3-CQAL-O-sulfate and 4-CQAL-O-sulfate. The quantification of urinary hydroxycinnamate derivatives showed 3 and 4-CQAL-O-sulfates, which accounted for 4.4% of the 120 μ mol excreted, appeared in urine predominantly 0 to 5 h after coffee intake.

CGLs are less polar than their parent compounds and should be more permeable to the blood-brain barrier. Previous studies have shown specific binding sites for CGLs in brain cells.²⁰² A significant correlation between CGLs amount in coffee and neuron cell survival has been reported,²⁰³ suggesting a possible contribution of the CGLs to the increased protective effects against H₂O₂-induced death of neuron cells. Apart from the antioxidant properties of the CGA lactones, these coffee compounds have been associated to enhancement of whole-body insulin action *in vivo*,²⁰⁴ anti-opioid activity³⁷ and high affinity with human serum albumin.²⁰⁵

In conclusion, coffee lactones might play an important role in chronic neurodegenerative disorders such as Alzheimer's and Parkinson's diseases, characterized by the loss of the neurons over the years. Further

investigation is needed to gain insight into the possible mechanisms of action of the coffee lactones and their effect on chronic pathologies.

X.3.1.3. Pyridines

N-methylpyridinium (NMP) is a non-volatile pyrolytic product generated upon coffee roasting by decarboxylation of trigonelline.²⁰⁶ This compound is a quaternary ammonium compound derived from the N-methylation of pyridine (Figure X.7).

Lang *et al.*²⁰⁷ quantified the concentrations of these pyridine derivatives in medium dark coffee brew as well as in plasma and urine samples of 13 healthy volunteers after coffee consumption. Coffee brew contained about 491 mM of NMP and after consumption of 350 ml freshly prepared coffee brew, plasma concentrations of NMP raised from virtually complete absence to maximum values of 777 (females) or 804 nmol/l (males) within 1-2 h. The high plasma levels of NMP demonstrated that this cation was entering the vascular system, which is the prerequisite for biological *in vivo* effects claimed for that compound. Interestingly, NMP is hardly metabolized and nearly 70% of the ingested dose is excreted about 8 h after coffee consumption. However, NMP can be detected in the urine up to 72 h post-load.²⁰⁷

Antioxidant health benefits of NMP have been previously proposed.³¹ NMPs showed weak potential as radical scavengers (TEAC assay) and against cellular ROS generation, however, were found to diminish menadione-induced DNA oxidation damage in Caco-2 cells. Highest effectiveness was exhibited by NM-2MP which achieved a maximal reduction of 68% at 3mM. On the other hand, Boettler *et al.*²⁰⁸ demonstrated that NMPs represent potent activators of Nrf2-nuclear translocation and subsequent antioxidant response element (ARE)-dependent gene transcription in human colon carcinoma cells (HT29) and therefore, exhibiting chemopreventive action.

Therefore, pyridines present in coffee beverage seem to exhibit potential benefits on chronic diseases related to cellular DNA damage. Further research is required to confirm their biological effects on the reduction of the risk of chronic diseases.

X.3.2. Volatile compounds of roasted coffee

Roasted coffee is an enormous source of low molecular weight (LMW) volatile compounds, particularly more than 300 heterocyclic compounds, which have recently begun to receive much attention as antioxidants, besides their contribution to aroma and flavor.²⁰⁹

It is difficult to determine all the reactions involved in the formation of volatile compounds, since a number of them may be produced by more than one route. Generally, carbohydrates produce furans, aldehydes, ketones, and phenols; proteins, peptide, and amino acids produce ketones, pyrrols, and pyrazines; lipids are responsible for only small amounts of aldehydes and ketones given their resistance to changes during the roasting process; CGAs

produce phenolic volatile compounds (e.g., catechols, pyrogallol, and phenol); and trigonelline produces pyrroles, pyridines, and pyrazines. Almost all thiophenes, oxazoles, and thiazoles are formed during roasting, since they are not usually detected in green coffee.⁵ Among them, pyrroles and furans have showed the strongest antioxidant activity, which was almost equal to that of α -tocopherol.²¹⁰

X.3.2.1. Furans and related structures

Furan is a small heterocyclic organic compound (Figure X.7).²¹¹ Ariseto *et al.*²¹² investigated furan formation in coffee and reported that glucose, sucrose, and polyunsaturated fatty acids (specifically linoleic and linolenic acids) are present in green coffee as potential precursors for furan formation in roasted coffee. However, it was hypothesized that other factors such as pH might also influence furan formation. The range of furan levels in roasted coffee have been reported from less than 1000 to 7000 $\mu\text{g}/\text{kg}$.²¹¹

The main furan compound generated in roasted coffee is 5-hydroxymethylfurfural (5-(hydroxymethyl)furan-2-carbaldehyde, HMF), which forms as an intermediate in the Maillard Reaction and from direct dehydration of sugars under acidic conditions (caramelisation) during thermal treatments²¹³ (Figure X.7). From 1,2 enolisation and dehydration of glucose or fructose, 3-deoxyosone is formed as the key intermediate and its further dehydration and cyclization yields 5-HMF. Under dry and pyrolytic conditions an alternative pathway to HMF formation from fructose and sucrose has been proposed, involving a highly reactive fructofuranosyl cation which can be directly converted to HMF.²¹⁴

According to the bioavailability of HMF, experiments involving administration of [^{14}C]-HMF via oral gavage showed that HMF is rapidly absorbed from the gastrointestinal tract in rats and mice and excreted primarily via the urine although some covalent binding has been reported in kidney, bladder and to a minor extent in liver.^{215,216} In Caco-2 cell line, the absorption and transport of HMF is higher when cells are exposed to higher HMF concentration. In addition, food composition i.e. fiber content may affect HMF uptake.²¹⁷ Moreover, it has been postulated that HMF that escapes gastrointestinal digestion could be converted to furfuryl alcohol to some extent by enteric bacterial strains.²¹⁸

Despite the previous progress reviewed on the dangers of 5-HMF,²¹³ there is an accepted theory concerning the biological activity of 5-HMF in recent years. The antioxidant activity of coffee 5-HMF has been widely reported *in vitro*.^{219,220} Zhao *et al.*²²⁰ described that HMF acted by scavenging the ABTS and DPPH free radicals and inhibiting AAPH-induced ROS generation on erythrocytes. 5-HMF caused an increase of the antioxidant enzymes activity (superoxide dismutase (SOD), glutathione peroxidase (GPx) and catalase (CAT)) which can individually or synergistically effect the removal of free radicals from the body. Reduction of the content of lipid peroxidation end product (MDA) was also reported and consequently, decreased free radical attack on the cytomembrane. Moreover, inhibition of ROS generation was observed with the addition of 5-HMF. These results suggest that 5-

HMF may cut off the reaction of lipid peroxidation from the source, increase endogenous antioxidant enzyme activity, protect the body from free radical attack, and maintain the integrity of the cell structure and function.

In conclusion, furans of the coffee beverage such as 5-HMF, seem to affect positively some chronic diseases by the protection from radical oxygen species. Further investigation *in vivo* is needed to confirm these preliminary studies.

X.3.2.2. Pyrroles, thiazoles and their derivatives

A number of heterocyclic compounds, including 1-methylpyrrole (Figure X.7) and derivatives, as well as thiazole (Figure X.7) and thiazole derivatives, have been identified in brewed roasted coffee.¹⁴⁴ To date, there are not studies describing the bioavailability and metabolism of these roasted coffee compounds. However, several reports have described their antioxidant effect. These constituents were effective at inhibiting heat-induced hexanol oxidation *in vitro*, a primary lipid oxidation product, thus confirming anti-peroxidation activity.²¹⁰ Pyrrole and related compounds have also been shown to react with hydroxyl radicals using EPR analysis.²²¹ The relative antioxidant activity of such components in coffee was not as strong as synthetic antioxidant butylated hydroxytoluene (BHT). However, because of important number of these heterocyclic compounds are present in coffee, their combined activity might be comparable to those of known antioxidants.²¹⁰

In order to gain more knowledge about these antioxidant volatile compounds of the coffee and their potential on the prevention of chronic pathologies, further research should be completed.

X.3.2.3. Phenolic volatile compounds

With a longer roasting time, the phenolic and quinic moieties start rapidly degrading such diverse phenolic components as 4-vinyl, ethyl-catechol and catechol from the phenolic moiety, and slowly degrading, hydroquinone, catechol, phenol and pyrogallol from the quinic moiety²²² (Figure X.7).

Regarding the bioavailability of pyrocatechol, studies have demonstrated that this compound from roast coffee is readily absorbed from the gastrointestinal tract. Part of the catechol conjugates in the body with glucuronic, sulfuric, and other acids and is excreted in the urine, with a little "free" pyrocatechol. The conjugates hydrolyze easily in the urine with the liberation of the "free" catechol, which is oxidized by air with the formation of dark-colored substances that impart to the urine a "smokey" appearance.²²³

Pyrocatechol presented high peroxy radical scavenging capacity measured by ORAC method but in contrast less efficiency to reduce ABTS radical (TEAC). In addition, slight effect of catechol on lowering TBH-induced ROS level in HT 29 cells after 24-h incubation was observed, suggesting cellular defense.³¹ On the other hand,

Kamiyama *et al.*²²⁴ described that heat, in particular, coffee roasting produced relatively high levels of pyrocatechol (2,809 µg/g) and 2-methoxy-4-vinylphenol (46 µg/g) from 5-CQA, and their antioxidant activity levels were 76.6% and 98.6%, respectively, in terms of free radical scavengers (DPPH method). These results suggest that roasting degrades CGAs to form potent antioxidants and thus plays an important role in the preparation of high-antioxidant low-acid coffee.

Such phenolic volatile compounds present in coffee could reduce oxidative damage and therefore might prevent or delay the development of cancer. Further studies are required to elucidate the beneficial impact on human health.

X.4. Conclusions

Coffee is one the most important source of dietary antioxidants in humans. The beverage is composed by a synergic mixture of antioxidants able to act following different mechanism of action. CGA was for a long time considered the unique antioxidant of the coffee beverage. The synergic combination of natural and processing antioxidants is responsible for the health promoting benefits of coffee brew. Since coffee natural antioxidants should be present in by-products during coffee processing more studies are necessary to add-value to them (see chapter 12). Several studies support coffee reduces the risk of chronic diseases considered global emergency like diabetes. The health promoting effect has been associated to coffee antioxidants.

Acknowledgements

The SUSCOFFEE Project (AGL2014-57239-R): Sustainable coffee production and consumption: Valorization of coffee waste into food ingredients funded this work. Fernandez-Gomez, B. is a fellow of the FPI predoctoral program of MINECO (BES-2011-046827). Martinez-Saez, N. thanks the Autonomous University of Madrid (UAM), Spain, for her FPI-predoc fellowship. Iriondo-DeHond, A. is a fellow of the FPI predoctoral program of the Ministry of Economy and Competitiveness (BES-2015-072191). Rebollo-Hernanz, M. thanks the JAE Intro fellowship (JAEINT_15_00086) and the FPU predoctoral program of the Ministry of Education, Culture and Sports (FPU15/04238).

References

- 1 T. Torres and A. Farah, *Eur. J. Nutr.*, 2016.
- 2 M. D. del Castillo, M. H. Gordon and J. M. Ames, *Eur. Food Res. Technol.*, 2005, **221**, 471–477.

- 3 R. C. Borrelli, A. Visconti, C. Mennella, M. Anese and V. Fogliano, *J. Agric. Food Chem.*, 2002, **50**, 6527–33.
- 4 R. C. Alves, I. M. Almeida, S. Casal and M. B. Oliveira, *J. Agric. Food Chem.*, 2010, **58**, 3002–7.
- 5 A. Farah, *Coffee Emerg. Heal. Eff. Dis. Prev.*, 2012, 21–58.
- 6 R. C. Alves, S. Casal and M. B. P. P. Oliveira, *J. Food Compos. Anal.*, 2010, **23**, 802–808.
- 7 P. Pohl, E. Stelmach, M. Welna and A. Szymczycha-Madeja, *Food Anal. Methods*, 2013, **6**, 598–613.
- 8 A. Ramakrishna, P. Giridhar, K. U. Sankar and G. A. Ravishankar, *J. Pineal Res.*, 2012, **52**, 470–6.
- 9 C. Campa, S. Doulbeau, S. Dussert, S. Hamon and M. Noiro, *Food Chem.*, 2005, **91**, 633–637.
- 10 * Myriam Richelle, and Isabelle Tavazzi and E. Offord, 2001.
- 11 D. Y. Kwon, K. H. Choi, S. J. Kim, D. W. Choi, Y. S. Kim and Y. C. Kim, *Arch. Pharm. Res.*, 2009, **32**, 283–7.
- 12 *,† Ronald L. Prior, † and Xianli Wu and K. Schaich§, 2005.
- 13 A. Yashin, Y. Yashin, J. Y. Wang and B. Nemzer, 2013, 230–245.
- 14 *,† José Ángel Gómez-Ruiz, ‡ and David S. Leake and §. Jennifer M. Ames†, 2007.
- 15 F. Saura-Calixto and I. Goñi, *Food Chem.*, 2006, **94**, 442–447.
- 16 A. Yashin, Y. Yashin, J. Wang and B. Nemzer, *Antioxidants*, 2013, **2**, 230–245.
- 17 M. D. del Castillo, B. Fernandez-Gomez, N. Martinez-Saez, A. Iriondo-DeHond, D. M. Martirosyan and M. D. Mesa, in *Functional Foods In Health And Disease*, ed. D. M. Martirosyan, 2016.
- 18 * Fausta Natella, Mirella Nardini, Irene Giannetti, and Cristina Dattilo and C. Scaccini, 2002.
- 19 G. M. Agudelo-Ochoa, I. C. Pulgarin-Zapata, C. M. Velasquez-Rodriguez, M. Duque-Ramirez, M. Naranjo-Cano, M. M. Quintero-Ortiz, O. J. Lara-Guzman and K. Munoz-Durango, *J. Nutr.*, 2016, **146**, 524–531.
- 20 I. A. Ludwig, M. N. Clifford, M. E. J. Lean, H. Ashihara and A. Crozier, *Food Funct.*, 2014, **5**, 695–1717.
- 21 M. S. H. Akash, K. Rehman and S. Chen, *Nutrition*, 2014, **30**, 755–763.
- 22 X. Jiang, D. Zhang and W. Jiang, *Eur. J. Nutr.*, 2014, **53**, 25–38.
- 23 R. M. Van Dam, *Nutr. Metab. Cardiovasc. Dis.*, 2006, **16**, 69–77.

- 24 J. S. Bonita, M. Mandarano, D. Shuta and J. Vinson, *Pharmacol. Res.*, 2007, **55**, 187–98.
- 25 A. Nehlig, *Pract. Neurol.*, 2016, **16**, 89–95.
- 26 S. Hall, B. Desbrow, S. Anoopkumar-Dukie, A. K. Davey, D. Arora, C. McDermott, M. M. Schubert, A. V. Perkins, M. J. Kiefel and G. D. Grant, *Food Res. Int.*, 2015, **76**, 626–636.
- 27 L. Wang, X. Shen, Y. Wu and D. Zhang, *Aust. N. Z. J. Psychiatry*, 2016, **50**, 228–42.
- 28 G. W. Ross, R. D. Abbott, H. Petrovitch, D. M. Morens, A. Grandinetti, K.-H. Tung, C. M. Tanner, K. H. Masaki, P. L. Blanchette, J. D. Curb, J. S. Popper and L. R. White, *JAMA*, 2000, **283**, 2674.
- 29 J. L. B. Quintana, M. F. Allam, A. S. Del Castillo and R. F.-C. Navajas, *Neurol. Res.*, 2007, **29**, 91–95.
- 30 C. S. de Magalhães, J. E. Takarada, N. C. Carvalho, D. do C. Carvalho, F. L. de Andrade, E. B. Ferreira, P. O. Luccas, L. Azevedo, C. S. de Magalhães, J. E. Takarada, N. C. Carvalho, D. do C. Carvalho, F. L. de Andrade, E. B. Ferreira, P. O. Luccas, L. Azevedo, lia Costa, D. do C. Carvalho, F. L. de Andrade, E. B. Ferreira, P. O. Luccas and L. Azevedo, *J. Chem.*, 2016, **2016**, 1–9.
- 31 T. Bakuradze, R. Lang, T. Hofmann, H. Stiebitz, G. Bytof, I. Lantz, M. Baum, G. Eisenbrand and C. Janzowski, *Mol. Nutr. Food Res.*, 2010, **54**, 1734–1743.
- 32 E. Loftfield, N. D. Freedman, B. I. Graubard, K. A. Guertin, A. Black, W.-Y. Huang, F. M. Shebl, S. T. Mayne and R. Sinha, *Am. J. Epidemiol.*, 2015, **182**, 1010–22.
- 33 A. Farah and T. F. Dos Santos, in *Coffee in Health and Disease Prevention*, ed. V. R. Preedy, London, Academic P., 2014, pp. 5–10.
- 34 J.-K. Moon, H. S. Yoo and T. Shibamoto, *J. Agric. Food Chem.*, 2009, **57**, 5365–9.
- 35 M. Daglia, A. Papetti, C. Gregotti, F. Bertè and G. Gazzani, *J. Agric. Food Chem.*, 2000, **48**, 1449–1454.
- 36 M. D. del Castillo, J. M. Ames and M. H. Gordon, *J. Agric. Food Chem.*, 2002, **50**, 3698–3703.
- 37 T. de Paulis, P. Commers, A. Farah, J. Zhao, M. P. McDonald, R. Galici and P. R. Martin, *Psychopharmacology (Berl.)*, 2004, **176**, 146–53.
- 38 A. Farah and G. Duarte, in *Coffee in Health and Disease Prevention*, ed. V. R. Preedy, Academic Press, London, 2014, pp. 789–801.
- 39 S. Lafay, C. Morand, C. Manach, C. Besson and A. Scalbert, *Br. J. Nutr.*, 2006, **96**, 39–46.
- 40 Y. Konishi and S. Kobayashi, *J. Agric. Food Chem.*, 2004, **52**, 2518–26.
- 41 M. Nardini, E. Cirillo, F. Natella and C. Scaccini, *J. Agric. Food Chem.*, 2002, **50**, 5735–5741.

- 42 S.-G. Lee, in *Coffee in Health and Disease Prevention*, ed. V. R. Preedy, London, 2014, pp. 913–920.
- 43 H. Kikuzaki, M. Hisamoto, K. Hirose, K. Akiyama and H. Taniguchi, *J. Agric. Food Chem.*, 2002, **50**, 2161–2168.
- 44 S. Foley, S. Navaratnam, D. J. McGarvey, E. J. Land, T. G. Truscott and C. A. Rice-Evans, *Free Radic. Biol. Med.*, 1999, **26**, 1202–1208.
- 45 C.-T. Yeh, L.-C. Ching and G.-C. Yen, *J. Nutr. Biochem.*, 2009, **20**, 163–71.
- 46 K. A. Kang, K. H. Lee, R. Zhang, M. Piao, S. Chae, K. N. Kim, Y. J. Jeon, D. B. Park, H. J. You, J. S. Kim and J. W. Hyun, *Biol. Pharm. Bull.*, 2006, **29**, 1820–1824.
- 47 K. L. Khanduja, P. K. Avti, S. Kumar, N. Mittal, K. K. Sohi and C. M. Pathak, *Biochim. Biophys. Acta*, 2006, **1760**, 283–9.
- 48 A. R. Sudheer, S. Muthukumaran, N. Devipriya, H. Devaraj and V. P. Menon, *Toxicology*, 2008, **243**, 317–29.
- 49 L. Y. Zang, G. Cosma, H. Gardner, X. Shi, V. Castranova and V. Vallyathan, *Am. J. Physiol. Cell Physiol.*, 2000, **279**, C954–60.
- 50 J. Psotová, S. Chlopčíková, P. Míketová, J. Hrbáč and V. Simánek, *Phytother. Res.*, 2004, **18**, 516–21.
- 51 U. J. Jung, M.-K. Lee, Y. B. Park, S.-M. Jeon and M.-S. Choi, *J. Pharmacol. Exp. Ther.*, 2006, **318**, 476–83.
- 52 S. Ramos, *Mol. Nutr. Food Res.*, 2008, **52**, 507–526.
- 53 R. Feng, Y. Lu, L. L. Bowman, Y. Qian, V. Castranova and M. Ding, *J. Biol. Chem.*, 2005, **280**, 27888–95.
- 54 S. K. Bøhn, R. Blomhoff and I. Paur, *Mol. Nutr. Food Res.*, 2014, **58**, 915–930.
- 55 S.-H. Kwon, H.-K. Lee, J.-A. Kim, S.-I. Hong, H.-C. Kim, T.-H. Jo, Y.-I. Park, C.-K. Lee, Y.-B. Kim, S.-Y. Lee and C.-G. Jang, *Eur. J. Pharmacol.*, 2010, **649**, 210–7.
- 56 M. Teraoka, K. Nakaso, C. Kusumoto, S. Katano, N. Tajima, A. Yamashita, T. Zushi, S. Ito and T. Matura, *J. Clin. Biochem. Nutr.*, 2012, **51**, 122–7.
- 57 W. Zhang, E. Lopez-Garcia, T. Y. Li, F. B. Hu and R. M. van Dam, *Diabetes Care*, 2009, **32**, 1043–5.
- 58 T. Bakuradze, N. Boehm, C. Janzowski, R. Lang, T. Hofmann, J.-P. Stockis, F. W. Albert, H. Stiebitz, G. Bytof, I. Lantz, M. Baum and G. Eisenbrand, *Mol. Nutr. Food Res.*, 2011, **55**, 793–797.

- 59 L. U. Thompson, B. A. Boucher, Z. Liu, M. Cotterchio and N. Kreiger, *Nutr. Cancer*, 2006, **54**, 184–201.
- 60 R. C. Alves, C. M. D. Soares and B. Oliveira, in *Coffee in Health and Disease Prevention*, ed. V. R. Preedy, London, 2014.
- 61 B. D. Oomah and F. S. Hosseinian, in *Methods of Analysis for Functional Foods and Nutraceuticals*, ed. W. J. Hurst, Taylor and Francis Group LLC/CRC Press, Boca Raton, 2nd edn., 2007.
- 62 F. Rafii, *Metabolites*, 2015, **5**, 56–73.
- 63 K. D. R. Setchell, N. M. Brown and E. Lydeking-Olsen, *J. Nutr.*, 2002, **132**, 3577–3584.
- 64 M. Messina and V. Messina, *J. Ren. Nutr.*, 2000, **10**, 63–8.
- 65 C. A. Rice-Evans, N. J. Miller, P. G. Bolwell, P. M. Bramley and J. B. Pridham, *Free Radic. Res.*, 1995, **22**, 375–83.
- 66 M. B. Ruiz-Larrea, A. R. Mohan, G. Paganga, N. J. Miller, G. P. Bolwell and C. A. Rice-Evans, *Free Radic. Res.*, 1997, **26**, 63–70.
- 67 B. Halliwell, J. Rafter and A. Jenner, *Am. J. Clin. Nutr.*, 2005, **81**, 268S–276S.
- 68 H. Wei, R. Bowen, Q. Cai, S. Barnes and Y. Wang, *Proc. Soc. Exp. Biol. Med.*, 1995, **208**, 124–30.
- 69 S. Kapiotis, M. Hermann, I. Held, C. Seelos, H. Ehringer and B. M. K. Gmeiner, *Arterioscler. Thromb. Vasc. Biol.*, 1997, **17**, 2868–2874.
- 70 N. A. Panat, D. K. Maurya, S. S. Ghaskadbi and S. K. Sandur, *Food Chem.*, 2016, **194**, 32–45.
- 71 A. Farah and C. M. Donangelo, *Brazilian J. Plant Physiol.*, 2006, **18**, 23–36.
- 72 E. R. B. a Prata and L. S. Oliveira, *LWT - Food Sci. Technol.*, 2007, **40**, 1555–1560.
- 73 P. S. Murthy, M. R. Manjunatha, G. Sulochannama and M. M. Naidu, *Eur. J. Biol. Sci.*, 2012, **4**, 13–19.
- 74 M. T. Satué-Gracia, M. Heinonen and E. N. Frankel, *J. Agric. Food Chem.*, 1997, **45**, 3362–3367.
- 75 H. Wang, G. Cao and R. L. Prior, *J. Agric. Food Chem.*, 1997, **45**, 304–309.
- 76 M. C. Guerra, F. Galvano, L. Bonsi, E. Speroni, S. Costa, C. Renzulli and R. Cervellati, *Br. J. Nutr.*, 2005, **94**, 211–20.
- 77 S. Talavéra, C. Felgines, O. Texier, C. Besson, J.-L. Lamaison and C. Rémésy, *J. Nutr.*, 2003, **133**, 4178–82.
- 78 F. Galvano, L. La Fauci, P. Vitaglione, V. Fogliano, L. Vanella and C. Felgines, *Ann. Ist. Super. Sanita*,

2007, **43**, 382–393.

- 79 R. B. Teponno, S. Kusari and M. Spiteller, *Nat. Prod. Rep.*, 2016.
- 80 J. Peterson, J. Dwyer, H. Adlercreutz, A. Scalbert, P. Jacques and M. L. McCullough, *Nutr. Rev.*, 2010, **68**, 571–603.
- 81 I. E. J. Milder, E. J. M. Feskens, I. C. W. Arts, H. B. B. de Mesquita, P. C. H. Hollman and D. Kromhout, *J. Nutr.*, 2005, **135**, 1202–1207.
- 82 G. G. C. Kuhnle, C. Dell'Aquila, S. M. Aspinall, S. A. Runswick, A. A. Mulligan and S. A. Bingham, *J. Agric. Food Chem.*, 2008, **56**, 7311–5.
- 83 M. Axelson, J. Sjövall, B. E. Gustafsson and K. D. R. Setchell, *Nature*, 1982, **298**, 659–660.
- 84 S. Heinonen, T. Nurmi, K. Liukkonen, K. Poutanen, K. Wähälä, T. Deyama, S. Nishibe and H. Adlercreutz, *J. Agric. Food Chem.*, 2001, **49**, 3178–86.
- 85 T. Nurmi, S. Voutilainen, K. Nyssönen, H. Adlercreutz and J. T. Salonen, *J. Chromatogr. B. Analyt. Technol. Biomed. Life Sci.*, 2003, **798**, 101–10.
- 86 K. Prasad, *Mol. Cell. Biochem.*, 1997, **168**, 117–23.
- 87 S. Ikeda, M. Kagaya, K. Kobayashi, T. Tohyama, Y. Kiso, N. Higuchi and K. Yamashita, *J. Nutr. Sci. Vitaminol. (Tokyo)*, 2003, **49**, 270–6.
- 88 K. Prasad, *Int. J. Angiol.*, 2000, **9**, 220–225.
- 89 R. Hatfield and W. Vermerris, *Plant Physiol.*, 2001, **126**, 1351–7.
- 90 J. W. De Vries, *Proc. Nutr. Soc.*, 2012, **62**, 37–43.
- 91 A. García, M. González Alriols, G. Spigno and J. Labidi, *Biochem. Eng. J.*, 2012, **67**, 173–185.
- 92 Y. Mukai, T. Norikura, S. Fujita, K. Mikame, M. Funaoka and S. Sato, *Mol. Cell. Biochem.*, 2011, **348**, 117–24.
- 93 S. Sato, Y. Mukai, J. Yamate, T. Norikura, Y. Morinaga, K. Mikame, M. Funaoka and S. Fujita, *Free Radic. Res.*, 2009, **43**, 1205–13.
- 94 P. T. Martone, J. M. Estevez, F. Lu, K. Ruel, M. W. Denny, C. Somerville and J. Ralph, *Curr. Biol.*, 2009, **19**, 169–75.
- 95 C. Pouteau, P. Dole, B. Cathala, L. Averous and N. Boquillon, *Polym. Degrad. Stab.*, 2003, **81**, 9–18.
- 96 S. Laurichesse and L. Avérous, *Prog. Polym. Sci.*, 2014, **39**, 1266–1290.

- 97 F. Saura-Calixto, *J. Agric. Food Chem.*, 2011, **59**, 43–49.
- 98 T. W. M. Crozier, A. Stalmach, M. E. J. Lean and A. Crozier, *Food Funct.*, 2012, **3**, 30–3.
- 99 D. Komes and A. Belščak-Cvitanović, in *Processing and Impact on Antioxidants in Beverages*, Elsevier, 2014, pp. 87–97.
- 100 A. Santini, R. Ferracane, P. Mikušová, Š. Eged, A. Šrobárová, G. Meca, J. Mañes and A. Ritieni, *Food Control*, 2011, **22**, 1240–1245.
- 101 T. Niseteo, D. Komes, A. Belščak-Cvitanović, D. Horžić and M. Budeč, *Food Chem.*, 2012, **134**, 1870–1877.
- 102 X. Shi, N. S. Dalal and a. C. Jain, *Food Chem. Toxicol.*, 1991, **29**, 1–6.
- 103 R. Lang, N. Dieminger, A. Beusch, Y.-M. Lee, A. Dunkel, B. Suess, T. Skurk, A. Wahl, H. Hauner and T. Hofmann, *Anal. Bioanal. Chem.*, 2013, **405**, 8487–8503.
- 104 M. J. Arnaud, Springer Berlin Heidelberg, 2011, pp. 33–91.
- 105 S. Azam, N. Hadi, N. U. Khan and S. M. Hadi, *Med. Sci. Monit.*, 2003, **9**, BR325–30.
- 106 J. Á. Gómez-Ruiz, D. S. Leake and J. M. Ames, *J. Agric. Food Chem.*, 2007, **55**, 6962–6969.
- 107 J. R. León-Carmona and A. Galano, *J. Phys. Chem. B*, 2011, **115**, 4538–4546.
- 108 T. P. A. Devasagayam, J. P. Kamat, H. Mohan and P. C. Kesavan, *Biochim. Biophys. Acta - Biomembr.*, 1996, **1282**, 63–70.
- 109 C. Lee, *Clin. Chim. Acta*, 2000, **295**, 141–154.
- 110 A. Kriško, M. Kveder and G. Pifat, *Clin. Chim. Acta*, 2005, **355**, 47–53.
- 111 N. M. Wedick, A. M. Brennan, Q. Sun, F. B. Hu, C. S. Mantzoros and R. M. van Dam, *Nutr. J.*, 2011, **10**, 93.
- 112 A. L. Beatriz Fernandez-Gomez, M. U. Miryam Amigo-Benavent, M. Herrero, M. Á. Martín, M. D. Mesa and M. D. del Castillo, *J. Funct. Foods*, 2016, **Submitted**.
- 113 K. Kagami, H. Morita, K. Onda, T. Hirano and K. Oka, *J. Pharm. Pharmacol.*, 2008, **60**, 1161–1165.
- 114 L. Chen, M. Yu, T. Shen, J. Xia and B. L. Xu, *Genet. Mol. Res.*, 2015, **14**, 5724–30.
- 115 S. K. Abunasef, H. A. Amin and G. A. Abdel-hamid, 2014, **52**, 42–50.
- 116 J. V. Higdon and B. Frei, *Crit. Rev. Food Sci. Nutr.*, 2006, **46**, 101–123.

- 117 R. J. Reiter, D. X. Tan and A. Galano, *Physiology*, 2014, **29**, 325–333.
- 118 R. J. Reiter, D. X. Tan, C. Osuna and E. Gitto, *J. Biomed. Sci.*, **7**, 444–58.
- 119 D. Tan, R. Reiter, L. Manchester, M. Yan, M. El-Sawi, R. Sainz, J. Mayo, R. Kohen, M. Allegra and R. Hardeland, *Curr. Top. Med. Chem.*, 2002, **2**, 181–197.
- 120 C. Rodriguez, J. C. Mayo, R. M. Sainz, I. Antolin, F. Herrera, V. Martin and R. J. Reiter, *J. Pineal Res.*, 2004, **36**, 1–9.
- 121 D.-X. Tan, R. Hardeland, L. C. Manchester, A. Korkmaz, S. Ma, S. Rosales-Corral and R. J. Reiter, *J. Exp. Bot.*, 2012, **63**, 577–97.
- 122 A. Ramakrishna, P. Giridhar, K. U. Sankar and G. A. Ravishankar, *J. Pineal Res.*, 2012, **52**, 470–476.
- 123 M. Rebollo-Hernanz, B. Fernández-Gómez, M. Herrero, C. Sanchez-Puelles, Y. Aguilera, M. D. del Castillo and M. A. Martin-Cabrejas, in *EURO FOOD CHEM XVIII*, Madrid, 2015, p. 192.
- 124 H.-M. Zhang and Y. Zhang, *J. Pineal Res.*, 2014, **57**, 131–146.
- 125 R. Hardeland, *Endocrine*, 2005, **27**, 119–30.
- 126 D. Zephy and J. Ahmad, *Diabetes Metab. Syndr.*, 2015, **9**, 127–31.
- 127 R. VIANI and I. HORMAN, *J. Food Sci.*, 1974, **39**, 1216–1217.
- 128 C.-L. Ky, J. Louarn, S. Dussert, B. Guyot, S. Hamon and M. Noirot, *Food Chem.*, 2001, **75**, 223–230.
- 129 R. Lang, A. Wahl, T. Skurk, E. F. Yagar, L. Schmiech, R. Eggers, H. Hauner and T. Hofmann, *Anal. Chem.*, 2010, **82**, 1486–97.
- 130 S. Ogata, M. Takeuchi, S. Teradaira, N. Yamamoto, K. Iwata, K. Okumura and H. Taguchi, *Biosci. Biotechnol. Biochem.*, 2002, **1**, 641–645.
- 131 W. Yen, B. Wang, L. Chang and P. Duh, .
- 132 N. Hirakawa, R. Okauchi, Y. Miura and K. Yagasaki, .
- 133 T. Bakuradze, R. Lang, T. Hofmann, H. Stiebitz, G. Bytof, I. Lantz, M. Baum, G. Eisenbrand and C. Janzowski, *Mol. Nutr. Food Res.*, 2010, **54**, 1734–43.
- 134 S. Ilavenil, D. H. Kim, Y.-I. Jeong, M. V. Arasu, M. Vijayakumar, P. N. Prabhu, S. Srigopalram and K. C. Choi, *Asian Pac. J. Trop. Med.*, 2015, **8**, 263–268.
- 135 J.-Y. Zhou, S.-W. Zhou, J.-Y. Zhou and S.-W. Zhou, *Evidence-Based Complement. Altern. Med.*, 2012, **2012**, 1–8.

- 136 J. Zhou, S. Zhou and S. Zeng, *Fundam. Clin. Pharmacol.*, 2013, **27**, 279–87.
- 137 A. E. Ghule, S. S. Jadhav and S. L. Bodhankar, *Int. Immunopharmacol.*, 2012, **14**, 740–748.
- 138 M. Tharahaswari, N. Jayachandra Reddy, R. Kumar, K. C. Varshney, M. Kannan and S. Sudha Rani, *Mol. Cell. Biochem.*, 2014, **396**, 161–174.
- 139 J. A. Silva, N. Borges, A. Santos and A. Alves, *Food Anal. Methods*, 2012, **5**, 1404–1410.
- 140 F. G. Campanha, R. C. E. Dias and M. D. T. Benassi, *Coffee Sci.*, 2010, **5**, 87–96.
- 141 C. Zhang, R. Linforth and I. D. Fisk, *Food Res. Int.*, 2012, **49**, 27–31.
- 142 K. J. Lee and H. G. Jeong, *Toxicol. Lett.*, 2007, **173**, 80–87.
- 143 W. W. Huber, D. Schachner, E. Haslinger, W. Parzefall, B. Grasl-Kraupp, A. Hochreiter, H. Lang, S. V. Torti, F. M. Torti and R. Schulte-Hermann, *Cancer Res.*, 2006, **66**, 926–926.
- 144 N. Liang and D. D. Kitts, *Molecules*, 2014, **19**, 19180–19208.
- 145 S.-Y. Choi, K.-J. Lee, H.-G. Kim, E.-H. Han, Y.-C. Chung, N.-J. Sung and H.-G. Jeong, *Bull. Korean Chem. Soc.*, 2006, **27**, 1386–1392.
- 146 K. J. Lee, J. H. Choi and H. G. Jeong, *Food Chem. Toxicol.*, 2007, **45**, 2118–2125.
- 147 M. S. Butt and M. T. Sultan, *Crit. Rev. Food Sci. Nutr.*, 2011, **51**, 363–373.
- 148 A. G. González, F. Pablos, M. J. Martín, M. León-Camacho and M. S. Valdenebro, *Food Chem.*, 2001, **73**, 93–101.
- 149 M. OGAWA, C. KAMIYA and Y. IIDA, *Nippon SHOKUHIN KOGYO GAKKAISHI*, 1989, **36**, 490–494.
- 150 L. Packer, S. U. Weber and G. Rimbach, *J. Nutr.*, 2001, **131**, 369–373.
- 151 S. B. Nimse and D. Pal, *RSC Adv.*, 2015, **5**, 27986–28006.
- 152 M. S. Brewer, *Compr. Rev. Food Sci. Food Saf.*, 2011, **10**, 221–247.
- 153 M. Estévez and M. Heinonen, *J. Agric. Food Chem.*, 2010, **58**, 4448–4455.
- 154 G. Neunert, P. Górnaś, K. Dwiecki, A. Siger and K. Polewski, *Eur. Food Res. Technol.*, 2015, **241**, 749–757.
- 155 S. P. Fortmann, B. U. Burda, C. A. Senger, J. S. Lin and E. P. Whitlock, *Ann. Intern. Med.*, 2013, **159**, 824–834.
- 156 L. J. Teply and R. F. Prier, *J. Agric. Food Chem.*, 1957, **5**, 375–377.

- 157 M. Ashoori and A. Saedisomeolia, .
- 158 T. TOYOSAKI and T. MINESHITA, *J. Food Sci.*, 1988, **53**, 1851–1853.
- 159 T. Toyosaki, *J. Agric. Food Chem.*, 1992, **40**, 1727–1730.
- 160 M. Durusoy, E. Karagöz and K. Öztürk, *J. Nutr. Biochem.*, 2002, **13**, 598–602.
- 161 J. H. Zaidi, I. Fatima, M. Arif and I. H. Qureshi, *J. Radioanal. Nucl. Chem.*, 2005, **267**, 109–112.
- 162 W. P. C. Santos, V. Hatje, L. N. Lima, S. V. Trignano, F. Barros, J. T. Castro and M. G. A. Korn, *Microchem. J.*, 2008, **89**, 123–130.
- 163 V. Diwadkar-Navsariwala and A. M. Diamond, *J. Nutr.*, 2004, **134**, 2899–902.
- 164 H. Tapiero, D. . Townsend and K. . Tew, *Biomed. Pharmacother.*, 2003, **57**, 134–144.
- 165 E. E. Battin and J. L. Brumaghim, *Cell Biochem. Biophys.*, 2009, **55**, 1–23.
- 166 H. Traulsen, H. Steinbrenner, D. P. Buchczyk, L.-O. Klotz and H. Sies, *Free Radic. Res.*, 2004, **38**, 123–128.
- 167 M. Grembecka, E. Malinowska and P. Szefer, *Sci. Total Environ.*, 2007, **383**, 59–69.
- 168 J. F. Collins, in *Modern Nutrition in Health and Disease: Eleventh Edition*, 2012, pp. 206–216.
- 169 M. A. Johnson, J. G. Fischer and S. E. Kays, *Crit. Rev. Food Sci. Nutr.*, 1992, **32**, 1–31.
- 170 *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc*, National Academies Press, Washington, D.C., 2001.
- 171 J. C. King and R. J. Cousins, in *Modern Nutrition in Health and Disease: Eleventh Edition*, 2012, pp. 189–205.
- 172 B. L. O’Dell, *J. Nutr.*, 2000, **130**, 1432S–6S.
- 173 S. R. Powell, *J. Nutr.*, 2000, **130**, 1447S–54S.
- 174 A. Viarengo, B. Burlando, N. Ceratto and I. Panfoli, *Cell. Mol. Biol. (Noisy-le-grand).*, 2000, **46**, 407–17.
- 175 B. O’Dell and R. Sunde, *Handb. Nutr. Essent. Miner.*, 1997.
- 176 J. D. Aguirre and V. C. Culotta, *J. Biol. Chem.*, 2012, **287**, 13541–13548.
- 177 M. Coassin, F. Ursini and A. Bindoli, *Arch. Biochem. Biophys.*, 1992, **299**, 330–333.
- 178 D. Gniechwitz, N. Reichardt, E. Meiss, J. Ralph, H. Steinhart, M. Blaut and M. Bunzel, *J. Agric. Food*

Chem., 2008, **56**, 5960–5969.

- 179 A. S. P. Moreira, F. M. Nunes, M. R. Domingues and M. A. Coimbra, *Food Funct.*, 2012, **3**, 903–15.
- 180 C. Delgado-Andrade, J. A. Rufián-Henares and F. J. Morales, *J. Agric. Food Chem.*, 2005, **53**, 7832–7836.
- 181 V. Somoza, *Mol. Nutr. Food Res.*, 2005, **49**, 663–672.
- 182 J. a Rufián-henares and F. J. Morales, 2007, 10016–10021.
- 183 V. Faist and H. F. Erbersdobler, *Ann. Nutr. Metab.*, 2001, **45**, 1–12.
- 184 M. Fujimaki, S. Homma, N. Arakawa and I. Choten, *Agric. Biol. Chem.*, 1979, **43**, 497–503.
- 185 B. Cämmerer and L. W. Kroh, *Eur. Food Res. Technol.*, 2006, **223**, 469–474.
- 186 C. Delgado-Andrade and F. J. Morales, *J. Agric. Food Chem.*, 2005, **53**, 1403–1407.
- 187 F. J. Morales, *Anal. Chim. Acta*, 2005, **534**, 171–176.
- 188 F. J. Morales, V. Somoza and V. Fogliano, *Amino Acids*, 2012, **42**, 1097–1109.
- 189 F. M. Nunes and M. A. Coimbra, *J. Agric. Food Chem.*, 2007, **55**, 3967–3977.
- 190 A. P. Echavarría, J. Pagán and A. Ibarz, *Food Eng. Rev.*, 2012, **4**, 203–223.
- 191 L. Goya, C. Delgado-Andrade, J. a Rufián-Henares, L. Bravo and F. J. Morales, *Mol. Nutr. Food Res.*, 2007, **51**, 536–545.
- 192 M. Daglia, M. Racchi, A. Papetti, C. Lanni, S. Govoni and G. Gazzani, *J. Agric. Food Chem.*, 2004, **52**, 1700–1704.
- 193 P. Vitaglione, F. Morisco, G. Mazzone, D. C. Amoroso, M. T. Ribecco, A. Romano, V. Fogliano, N. Caporaso and G. D’Argenio, *Hepatology*, 2010, **52**, 1652–61.
- 194 N. Reichardt, D. Gniechwitz, H. Steinhart, M. Bunzel and M. Blaut, *Mol. Nutr. Food Res.*, 2009, **53**, 287–299.
- 195 T. A. Ullman and S. H. Itzkowitz, *Gastroenterology*, 2011, **140**, 1807–16.
- 196 K. Uchida, *Free Radic. Biol. Med.*, 2000, **28**, 1685–96.
- 197 J. M. Silvan, F. J. Morales and F. Saura-Calixto, *J. Agric. Food Chem.*, 2010, **58**, 12244–12249.
- 198 A. Farah, T. de Paulis, L. C. Trugo and P. R. Martin, *J. Agric. Food Chem.*, 2005, **53**, 1505–13.
- 199 A. Farah, M. Monteiro, C. M. Donangelo and S. Lafay, *J. Nutr.*, 2008, **138**, 2309–2315.

- 200 A. Stalmach, H. Steiling, G. Williamson and A. Crozier, *Arch. Biochem. Biophys.*, 2010, **501**, 98–105.
- 201 A. Stalmach, W. Mullen, D. Barron, K. Uchida, T. Yokota, C. Cavin, H. Steiling, G. Williamson and A. Crozier, *Drug Metab. Dispos.*, 2009, **37**, 1749–1758.
- 202 T. De Paulis, D. E. Schmidt, A. K. Bruchey, M. T. Kirby, M. P. McDonald, P. Commers, D. M. Lovinger and P. R. Martin, *Eur. J. Pharmacol.*, 2002, **442**, 215–223.
- 203 Y. F. Chu, P. H. Brown, B. J. Lyle, Y. Chen, B. M. Richard, C. E. Williams, Y. C. Lin, C. W. Hsu and I. H. Cheng, *J. Agric. Food Chem.*, 2009, **57**, 9801–9808.
- 204 J. Shearer, A. Farah, T. De Paulis, D. P. Bracy, R. R. Pencek, T. E. Graham and D. H. Wasserman, 2003, **1**, 3529–3532.
- 205 V. Sinisi, C. Forzato, N. Cefarin, L. Navarini and F. Berti, *Food Chem.*, 2015, **168**, 332–340.
- 206 R. Lang, A. Wahl, T. Stark and T. Hofmann, *ACS Symp. Ser.*, 2012, **1098**, 13–25.
- 207 R. Lang, A. Wahl, T. Stark and T. Hofmann, *Mol. Nutr. Food Res.*, 2011, **55**, 1613–1623.
- 208 U. Boettler, K. Sommerfeld, N. Volz, G. Pahlke, N. Teller, V. Somoza, R. Lang, T. Hofmann and D. Marko, *J. Nutr. Biochem.*, 2011, **22**, 426–440.
- 209 D. Komes and A. Bušić, in *Processing and Impact on antioxidants in Beverages*, ed. V. Preedy, Academic Press-Elsevier, London, 2014, pp. 25–32.
- 210 K. Yanagimoto, K. G. Lee, H. Ochi and T. Shibamoto, *J. Agric. Food Chem.*, 2002, **50**, 5480–5484.
- 211 H. Guenther, *Coffee Emerg. Heal. Eff. Dis. Prev.*, 2012, 307–318.
- 212 A. P. Ariseto, E. Vicente, M. S. Ueno, S. A. V. Tfouni and M. C. D. F. Toledo, *J. Agric. Food Chem.*, 2011, **59**, 3118–24.
- 213 E. Capuano and V. Fogliano, *LWT - Food Sci. Technol.*, 2011, **44**, 793–810.
- 214 C. Perez Locas and V. A. Yaylayan, *J. Agric. Food Chem.*, 2008, **56**, 6069–74.
- 215 J. E. Germond, G. Philippossian, U. Richli, I. Bracco and M. J. Arnaud, *J. Toxicol. Environ. Health*, 1987, **22**, 79–89.
- 216 V. B. Godfrey, L. J. Chen, R. J. Griffin, E. H. Lebetkin and L. T. Burka, *J. Toxicol. Environ. Health. A*, 1999, **57**, 199–210.
- 217 C. Delgado-Andrade, I. Seiquer, M. P. Navarro and F. J. Morales, *Food Chem. Toxicol.*, 2008, **46**, 1600–7.

- 218 R. Boopathy, H. Bokang and L. Daniels, *J. Ind. Microbiol.*, 1993, **11**, 147–150.
- 219 W. J. Yen, B. Sen Wang, L. W. Chang and P. Der Duh, *J. Agric. Food Chem.*, 2005, **53**, 2658–2663.
- 220 L. Zhao, J. Chen, J. Su, L. Li, S. Hu, B. Li, X. Zhang, Z. Xu and T. Chen, 2013.
- 221 a. Samuni and P. Neta, *J. Phys. Chem.*, 1973, **77**, 1–7.
- 222 V. Leloup, A. Louvrier and R. Liardon, *Proc. 16th Int. Sci. Coll. Coffee (Kyoto), Assoc. Sci. Int. du Cafe'*, 1995, 192–198.
- 223 E. Bingham, B. Cahrssen and C. H. Powell, in *Patty's Toxicology Volumes 1-9*, John Wiley & Sons, New York, 5th edn., 2001, pp. 4–401.
- 224 M. Kamiyama, J. K. Moon, H. W. Jang and T. Shibamoto, *J. Agric. Food Chem.*, 2015, **63**, 1996–2005.
- 225 T. Clavel, J. Doré and M. Blaut, *Nutr. Res. Rev.*, 2006, **19**, 187–96.

Figure Captions

Figure X.1. Representation of antioxidant compounds present in coffee.

Figure X.2. Isoflavones determined in coffee and their simplified metabolism.

Figure X.3. Main anthocyanins present in coffee.

Figure X.4. Structure of monolignols and formation of lignans and lignin.

Figure X.5. Metabolism of secoisolariciresinol the most abundant lignan plant lignin in coffee. Based on Clavel, Doré, & Blaut, 2006; Peterson *et al.*, 2010.

Figure X.6. Melatonin structure.

Figure X.7. Coffee processing antioxidants.